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10/584,770	06/28/2006	Ronit Sagi-Eisenberg	27514U	5786

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THE NATH LAW GROUP
112 South West Street
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EXAMINER	
JUNG, UNSU	
ART UNIT	PAPER NUMBER
1641	
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06/22/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/584,770	SAGI-EISENBERG, RONIT	
	Examiner	Art Unit	
	UNSU JUNG	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *5,6,15,27-30 and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-14,16-26 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 June 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's amendments in the reply filed on April 1, 2009 have been acknowledged and entered. The reply included amendments to claims 1-8, 10-14, 16-26, and 31.

Status of Claims

2. Claims 1-32 are pending, claims 5, 6, 15, 27-30, and 32 have been withdrawn from consideration, and claims 1-4, 7-14, 16-26, and 31 are currently under consideration for patentability under 37 CFR 1.104.

As a preliminary matter, a typo has been noted in the previous Office Action Summary (PTOL-326) dated December 1, 2008. The status of claims 27-30 as being withdrawn is inadvertently missing in the Disposition of Claims section. Claims 27-30 have previously withdrawn as a result of election/restriction (see previous Office Action dated December 1, 2008) and should have been indicated as withdrawn in the Disposition of Claims section of the Office Action Summary. This error is corrected in the current Office Action.

Priority

3. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. The instant application is a

national phase under 35 U.S.C. 371 of PCT International Application No. PCT/IL2004/001172, filed on December 29, 2004, which claims the benefit under 35 USC 119(e) U.S. Provisional Patent Application No. 60/532,552, filed on December 29, 2003.

Objections Withdrawn

4. The objection of the specification has been withdrawn in view of the amended specification in the reply filed on April 1, 2009.

Claim Objections

5. Claim 4 is objected to because of the following informalities: the word "and" should be inserted following the term "sperm" in line 3. Appropriate correction is required.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. Claims 1-4, 7-9, 13-17, and 20-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over MacFarlane et al. (U.S. Patent No. 5,650,288, July 22, 1997) (hereinafter "MacFarlane") in view of Chen et al. (U.S. Patent No. 4,385,126, May 24, 1983) (hereinafter "Chen") and Clackson et al. (U.S. Patent No. 6,187,757, Feb. 13 2001) (hereinafter "Clackson").

MacFarlane teaches that a major concern in immunosuppressive therapy associated with organ transplantation is the level of immunosuppressive drug circulating in the blood (see entire document, particularly column 1, lines 40-42). Toxicity can result if the immunosuppressive drug level is too high; graft rejection and opportunistic infection can result if the immunosuppressive drug level is too low (column 1, lines 42-45). MacFarlane et al. provides a method of assaying a sample of blood or blood components for the concentration of immunophilin ligand such as rapamycin using a variety of binding assays including receptor binding assay (column 2, lines 6-24).

With respect to claims 3, 4, and 7, MacFarland et al. teaches a sample, which is a clinical blood sample (column 1, lines 14-45).

With respect to claims 20 and 21, MacFarlane teaches a kit containing reagents for detection assay of immunophilins (column 6, lines 20-34).

With respect to claim 31, MacFarlane teaches use of standards, which would read on "pre-weighed samples of rapamycin" (column 5, line 61).

However, MacFarlane et al. fails to teach a method, wherein the receptor binding assays includes a sandwich format using immobilized FKBP12 and mTOR as a detecting receptor.

Chen teaches a well known method of sandwich assay, in which an assay ligand binds to an immobilized receptor ligand to form a first complex (see entire document, particularly column 1, lines 40-42). A tagged test ligand is then bound to the assay ligand in the complex to form the sandwich and the tagging constituent in the sandwiched ligands is detected quantitatively to deduce the quantity of assay ligand present. The detection can be performed by measuring radioactive, fluorescent, or enzyme labels present on the test ligand (column 1, lines 42-47). Furthermore, the quantity of assay ligand is deduced from quantity of test ligand detected using known standards (column 1, lines 58-62).

With respect to claims 13, 14, 16, 17, and 22-25, Chen et al. teaches that the test ligand (FRB fragment of Clackson set forth below) is directly bound to a detectable label/enzyme, which can be detected by spectrophotometry, fluorospectrophotometry, and radiospectrometry (column 1, lines 42-47).

With respect to claims 7-9, Clackson teaches that rapamycin binds to a FK506-binding protein (FKBP12, see entire document, particularly column 4, lines 57-62) with

high affinity to form a rapamycin:FKBP complex, which binds with high affinity to the FRB domain of large cellular protein FRAP (mTOR, column 7, lines 56-67) to form FKBP:rapamycin:FRAP complex (column 1, lines 13-21). A number of rapamycin variants have been synthetically produced to improve the compound's therapeutic index as an immunosuppressive agent (column 2, lines 4-7).

With respect to claims 13-14, and 22, Clackson teaches FRB fragment (column 95, line 53).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to utilize a sandwich assay method of Chen, which employs two receptors for a detection ligand using a standard curve, in the method of assaying a blood sample for immunosuppressive drug, rapamycin, as taught by MacFarlane in order to perform an assay to detect concentration of rapamycin using FKBP12 and mTOR of Clackson, which are known protein receptors of rapamycin. Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to use FKBP12 as the immobilizing receptor since FKBP12 binds to the rapamycin independent of mTOR, while mTOR binds to the FKBP12-rapamycin complex as taught by Clackson.

The advantage of using the sandwich assay method, which is well known in the binding assay art to be one of the most sensitive assays for detecting target analytes in the sample, provides the motivation for combining the methods of Chen Clackson, and MacFarlane as the two rapamycin binding proteins, FKBP12 and mTOR, have high affinity for rapamycin.

One of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in combining teachings of Chen, Clackson, and MacFarlane since MacFarland teaches that a variety of binding assays including receptor binding assay can be used to determine level of immunosuppressive drug circulating in the blood.

With respect to claim 2, Clackson et al. teaches that a variety of rapamycin analogs (synthetic) are used as a therapeutic agent (column 2, lines 4-22) and also bind to FKBP12 (column 4, lines 57-62) and mTOR (column 7, lines 31-67). Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to determine the concentration of rapamycin or rapamycin analog in patients in order to determine rapamycin analog levels in patients receiving rapamycin analogs as FKBP12 and mTOR form FKBP:rapamycin:FRAP complex in the presence of rapamycin or rapamycin analogs.

9. Claims 10, 12, 18, 19, and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over MacFarlane (U.S. Patent No. 5,650,288, July 22, 1997) in view of Chen (U.S. Patent No. 4,385,126, May 24, 1983) and Clackson (U.S. Patent No. 6,187,757, Feb. 13, 2001) as applied to claims 1, 3, 20, 22, and 25 above, and further in view of Hammock et al. (U.S. Patent No. 5,459,040, Oct. 17, 1995) (hereinafter "Hammock").

MacFarland in view of Chen and Clackson teaches an assay for determining rapamycin or rapamycin analog concentrations in a sample as set forth above.

However, MacFarland in view of Chen and Clackson fails to teach a method, wherein the solid support is a 96-well microtiter plate and the detection is achieved by an ELISA reader and the enzyme is horse radish peroxidase (HRP).

With respect to claims 10, 12, 18, 19, and 26, Hammock teaches that sandwich assay can be conducted using 96-well microtiter plates (see entire document, particularly column 5, lines 24-26) and that variety of different labels including HRP can be used for detection (column 10, lines 30-51). The 96-well microtiter plates can be read by ELISA plate readers (column 11, line 52-column 12, line 8) following color development using chromogenic substrates such as 3,3',5,5'-tetramethylbenzidine (column 10, lines 30-51).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to employ a 96 well microtiter plate, which detected by an ELISA reader, wherein HRP is used as an enzyme label with 3,3',5,5'-tetramethylbenzidine as a substrate as taught by Hammock in the method and kit of MacFarland in view of Chen and Clackson in order to perform sandwich assay for determining rapamycin concentrations in a sample.

The advantage conducting multiple sample analysis of rapamycin using 96-well microtiter plate with an ELISA reader, which is designed for reading 96-well plate, provides the motivation for combining the methods of MacFarland in view of Chen and Clackson.

In addition, one of ordinary skill in the art would have found it obvious to employ the HRP as an enzyme label with 3,3',5,5'-tetramethylbenzidine as a substrate as taught

by Hammock since it appears that any well know enzyme label and corresponding substrate such as HRP and p3,3',5,5'-tetramethylbenzidine would perform equally well with the assay method of MacFarland in view of Chen and Clackson.

10. Claims 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over MacFarlane (U.S. Patent No. 5,650,288, July 22, 1997) in view of Chen (U.S. Patent No. 4,385,126, May 24, 1983) and Clackson (U.S. Patent No. 6,187,757, Feb. 13, 2001) as applied to claims 1 and 3 above, and further in view of Coligan et al. (Current Protocols in Immunology, Vol. 1, 1991, John Wiley & Sons, Inc., pp2.1.1-2.1.22) (hereinafter "Coligan").

MacFarland in view of Chen and Clackson teaches an assay for determining rapamycin or rapamycin analog concentrations in a sample as set forth above. However, MacFarland in view of Chen and Clackson fails to teach a method, wherein the solid support is a 96-well microtiter plate, which is blocked by non specific protein, and the detection is achieved by an ELISA reader.

Coligan et al. teaches methods of variety of sandwich assays, which are typically conducted on a 96-well microtiter plates and read by an ELISA reader (p2.1.17, Fig. 2.1.7). Coligan et al. further teaches a blocking step, which blocks residual binding capacity of the plate following immobilization of capture antibody (p2.1.5, Block residual binding capacity of plate).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to employ a 96 well microtiter plate, which is blocked by

non specific protein and detected by an ELISA reader, as taught by Coligan in the method of MacFarland in view of Chen and Clackson in order to perform sandwich assay for determining rapamycin concentrations in a sample.

The advantage conducting multiple sample analysis of rapamycin using 96-well microtiter plate with an ELISA reader, which is designed for reading 96-well plate, provides the motivation for combining the methods of MacFarland in view of Chen and Clackson and Coligan.

Furthermore, one of ordinary skill in the art at the time of the invention would have recognized that blocking step of Coligan et al. is a necessary step in a sandwich assay to block binding of non specific proteins. Therefore, the advantage of including a blocking step in order to block binding of non specific proteins provides the motivation for combining the methods of MacFarland in view of Chen and Clackson and Coligan as the blocking step would increase the specificity of the assay of MacFarland in view of Chen and Clackson.

11. Claim 31 is rejected under 35 U.S.C. 103(a) as being unpatentable over MacFarlane (U.S. Patent No. 5,650,288, July 22, 1997) in view of Chen (U.S. Patent No. 4,385,126, May 24, 1983) and Clackson (U.S. Patent No. 6,187,757, Feb. 13, 2001) as applied to claims 20 and 22 above, and further in view of Abuknesha (U.S. Patent No. 5,723,304, Mar. 3, 1998).

MacFarland in view of Chen and Clackson teaches an assay for determining rapamycin or rapamycin analog concentrations in a sample as set forth above.

Clackson et al. further teaches that a variety of rapamycin analogs (synthetic) are used as a therapeutic agent (column 2, lines 4-22) and also bind to FKBP12 (column 4, lines 57-62) and mTOR (column 7, lines 31-67). Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to determine the concentration of rapamycin or rapamycin analog in patients in order to determine rapamycin analog levels in patients receiving rapamycin analogs as FKBP12 and mTOR form FKBP:rapamycin:FRAP complex in the presence of rapamycin or rapamycin analogs. However, MacFarland in view of Chen and Clackson fails to teach that pre-weighed samples of rapamycin analogs for producing calibration curves.

Abuknesha teaches that analyte species or analyte analog species can be used as standard or calibrator (column 1, line 58-column 2, line 2).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to further include rapamycin analogs as known standards with a reasonable expectation of success in order to determine rapamycin and/or rapamycin analog concentrations in a sample since Abuknesha teaches that analyte species or analyte analog species can be used as standard or calibrator.

Response to Arguments

12. Rejection of claims 1-4, 7-9, 13-17, and 20-25 under 35 U.S.C. 103(a) as being unpatentable over MacFarlane in view of Chen and Clackson

Applicant's arguments filed on April 1, 2009 have been fully considered but they are not persuasive essentially for the reasons of record and arguments addressed herein.

Applicant traverses the rejection because a *prima facie* case of obviousness has not been established because none of the references, either taken alone or in combination, teach or suggest all the elements of the present claims. Specifically, applicant asserts that none of the references, either taken alone or in combination, teach or suggest an assay for determining concentration of rapamycin or rapamycin analog in a sample, the rapamycin or rapamycin analog being capable of binding to FKBP12 protein or a binding domain thereof by contacting the sample with FKBP12 protein or with a rapamycin binding fragment of FKBP12 protein that maintains the rapamycin binding properties for a time period and under conditions allowing formation of rapamycin/FKBP12 complex and a kit for determining rapamycin concentrations, or rapamycin analog concentrations in a sample, the kit comprising: a FKBP12 protein or a rapamycin binding portion thereof immobilized on a solid substrate; and a complex-binding domain of mTOR linked to a label that may be detected or that may generate a signal, as recited in claim 20. However, applicant's arguments are not persuasive essentially for the reasons of record and arguments addressed herein

As stated in the previous Office Action dated December 1, 2008 (see item 8), MacFarlane teaches that a major concern in immunosuppressive therapy associated with organ transplantation is the level of immunosuppressive drug circulating in the blood (see entire document, particularly column 1, lines 40-42). Toxicity can result if the immunosuppressive drug level is too high; graft rejection and opportunistic infection can result if the immunosuppressive drug level is too low (column 1, lines 42-45). MacFarlane provides a method of assaying a sample of blood or blood components for

the concentration of immunophilin ligand such as rapamycin using a variety of binding assays including receptor binding assay (column 2, lines 6-24). The teachings of MacFarlane are further acknowledged by the applicant on p17 of the Remarks. However, MacFarlane et al. fails to teach a method, wherein the receptor binding assays includes a sandwich format using immobilized FKBP12 and mTOR as a detecting receptor.

Additionally, Applicant notes that MacFarlane et al. do not teach or suggest an assay for determining a drug concentration in the blood circulation. This argument is not found persuasive essentially for the reasons of record as MacFarlane teaches that a major concern in immunosuppressive therapy associated with organ transplantation is the level of immunosuppressive drug circulating in the blood (see entire document, particularly column 1, lines 40-42) and MacFarlane provides a method of assaying a sample of blood or blood components for the concentration of immunophilin ligand such as rapamycin using a variety of binding assays including receptor binding assay (column 2, lines 6-24).

Chen teaches a well known method of sandwich assay, in which an assay ligand binds to an immobilized receptor ligand to form a first complex (see entire document, particularly column 1, lines 40-42). A tagged test ligand is then bound to the assay ligand in the complex to form the sandwich and the tagging constituent in the sandwiched ligands is detected quantitatively to deduce the quantity of assay ligand present. The detection can be performed by measuring radioactive, fluorescent, or enzyme labels present on the test ligand (column 1, lines 42-47). Furthermore, the

quantity of assay ligand is deduced from quantity of test ligand detected using known standards (column 1, lines 58-62).

In contrast to applicant's assertions; disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. See *In re Susi*, USPQ 423 (CCPA 1971). A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use. See *In re Gurley*, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994). A prior art reference may be considered to teach away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." In re Gurley, 27 F.3d 551, 553, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994). General skepticism of those in the art -- not amounting to teaching away -- is also "relevant and persuasive evidence" of nonobviousness. Gillette Co. v. S.C. Johnson & Son, Inc., 919 F.2d 720, 726, 16 USPQ2d 1923, 1929 (Fed. Cir. 1990). In effect, "teaching away" is a more pointed and probative form of skepticism expressed in the prior art. See MPEP § 2123. Although Chen's teachings may indicate some variations in accuracy of various immunoassays, Chen does not discourage from using sandwich assay format. Therefore, the teachings of Chen do not constitute teaching away from employing sandwich assays.

Applicant's argument that the sandwich assay of Chen would result in an antibody that may recognize metabolites of rapamycin has been fully considered but it not found persuasive essentially for the reasons of record. In response to applicant's

arguments that the sandwich assay of Chen would result in an antibody that may recognize metabolites of rapamycin, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As stated in the previous Office Action dated December 1, 2008 (see item 8), Clackson teaches that rapamycin binds to a FK506-binding protein (FKBP12, see entire document, particularly column 4, lines 57-62) with high affinity to form a rapamycin:FKBP complex, which binds with high affinity to the FRB domain of large cellular protein FRAP (mTOR, column 7, lines 56-67) to form FKBP:rapamycin:FRAP complex (column 1, lines 13-21). A number of rapamycin variants have been synthetically produced to improve the compound's therapeutic index as an immunosuppressive agent (column 2, lines 4-7). Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to utilize a sandwich assay format of Chen, which employs two receptors for a detection ligand using a standard curve, in the method of assaying a blood sample for immunosuppressive drug, rapamycin, as taught by MacFarlane in order to perform an assay to detect concentration of rapamycin using FKBP12 and mTOR of Clackson, which are known protein receptors of rapamycin. Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to use FKBP12 as the immobilizing receptor since FKBP12 binds to the rapamycin independent of mTOR, while mTOR binds to the FKBP12-rapamycin complex as taught by Clackson. As such, the rejection is based on using the reagents of Clackson, not

antibodies of Chen, in order to conduct the sandwich assay for determination of rapamycin concentration.

The advantage of using the sandwich assay method, which is well known in the binding assay art to be one of the most sensitive assays for detecting target analytes in the sample, provides the motivation for combining the methods of Chen Clackson, and MacFarlane as the two rapamycin binding proteins, FKBP12 and mTOR, have high affinity for rapamycin. Toukatly et al. (U.S. Patent No. 5,686,562, Nov. 11, 1997) teaches that for serum and other fluid assays, one of the currently most sensitive immunoassay formats is the sandwich technique (column 7, lines 23-26). Similarly, Kindler (U.S. Patent No. 5,494,831, Feb. 27, 1996) teaches that one of the most sensitive of the immunoassays is the two-step sandwich type immunoradiometric assay (column 2, lines 17-23).

One of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in combining teachings of Chen, Clackson, and MacFarlane since MacFarland teaches that a variety of binding assays including receptor binding assay can be used to determine level of immunosuppressive drug circulating in the blood.

Therefore, the combined teachings of MacFarlane, Chen, and Clarkson read on the sandwich format assay of the claimed invention.

Applicant's argument regarding the teachings of U.S. Patent No. 6,635,745, which suggest a lack of sensitive and reliable assay for rapamycin which can be performed quickly and easily in a clinical setting has been fully considered but is not

found persuasive. Prior failure by another who did not have knowledge of the best art or was not motivated to try because of satisfaction with the way things were is not persuasive of nonobviousness. *In re Sneed*, 218 USPQ 385 (Fed. Cir. 1983). Further, prior failure by others to solve the problem solved by the claimed invention is not established where the prior effort was limited to investigation of the problem and its causes. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983). In addition, U.S. Patent No. 6,635,745 teaches that sandwich format assays can be employed to measure blood levels of rapamycin using antibodies (column 22, lines 1-16). Therefore, the teachings of U.S. Patent No. 6,635,745 do not constitute a departure from using sandwich assay format for measuring blood levels of rapamycin. As such, the combination of the references cited by the Examiner does not constitute a departure from the state of the art prior to the filing date of the present application.

In view of the foregoing response to arguments, the rejection of claims 1-4, 7-9, 13-17, and 20-25 under 35 U.S.C. 103(a) as being unpatentable over MacFarlane in view of Chen and Clackson has been maintained.

13. Rejection of claims 10, 12, 18, 19, and 26 under 35 U.S.C. 103(a) as being unpatentable over MacFarlane in view of Chen and Clackson, and further in view of Hammock

Applicant's arguments filed on April 1, 2009 have been fully considered but they are not persuasive essentially for the reasons of record and arguments addressed above.

In view of the foregoing response to arguments, the rejection of claims 1-4, 7-9, 13-17, and 20-25 under 35 U.S.C. 103(a) as being unpatentable over MacFarlane in view of Chen and Clackson has been maintained.

14. Rejection of claims 10-12 under 35 U.S.C. 103(a) as being unpatentable over MacFarlane in view of Chen and Clackson, and further in view of Coligan

Applicant's arguments filed on April 1, 2009 have been fully considered but they are not persuasive essentially for the reasons of record and arguments addressed above.

In view of the foregoing response to arguments, the rejection of claims 1-4, 7-9, 13-17, and 20-25 under 35 U.S.C. 103(a) as being unpatentable over MacFarlane in view of Chen and Clackson has been maintained.

15. Rejection of claim 31 under 35 U.S.C. 103(a) as being unpatentable over MacFarlane in view of Chen and Clackson, and further in view of Abuknesha

Applicant's arguments filed on April 1, 2009 have been fully considered but they are not persuasive essentially for the reasons of record and arguments addressed above.

In view of the foregoing response to arguments, the rejection of claims 1-4, 7-9, 13-17, and 20-25 under 35 U.S.C. 103(a) as being unpatentable over MacFarlane in view of Chen and Clackson has been maintained.

16. Since the prior art fulfills all the limitations currently recited in the claims, the invention as currently recited would read upon the prior art.

Conclusion

17. No claim is allowed.

18. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to UNSU JUNG whose telephone number is (571)272-8506. The examiner can normally be reached on M-F: 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached on 571-272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Unsu Jung/
Unsu Jung
Primary Examiner
Art Unit 1641